Original Long Version

# MEMORANDUM

DATE: DECEMBER 1, 1993

RE: ALAVANJA, M.C.R., BROWN, C.C., SWANSON, C., AND BROWNSON, R.C., "SATURATED FAT INTAKE AND LUNG CANCER RISK AMONG NONSMOKING WOMEN IN MISSOURI," JOURNAL OF THE NATIONAL CANCER INSTITUTE 85(23): 1906-1916, 1993

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## Overview

This long-anticipated study marks the third major publication based on data collected from a sample of nonsmoking female lung cancer cases in Missouri. The other papers have focused on ETS exposure (Brownson, et al., 1992)[1] and previous lung disease (Alavanja, et al., 1992)[2] as possible risk factors for lung cancer in nonsmokers.

In the current paper, the authors report on the possible effects of a "broad range of dietary factors" for lung cancer risk in their study population. They report a strongly elevated, statistically significant relative risk for the highest level of saturated fat consumption, a "protective" effect for bean and pea consumption, and an elevated risk associated with consumption of citrus fruit and juice. [Saturated fats are those fats that are solid at room temperature, e.g., meat fat, butter, lard, etc.]

The magnitude of the reported risk estimate for high saturated fat intake, an approximate six-fold increase when compared to the group reporting the lowest intake, is substantially higher than risks reported in other studies on dietary factors. The authors attribute this to the use of only nonsmoking women in the study, and to the large percentage of adenocarcinoma cases in their sample.

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1 Brownson, R.C., Alavanja, M.C.R., Hock, E.T., and Loy, T.S., "Passive Smoking and Lung Cancer in Nonsmoking Women," American Journal of Public Health 82: 1525-1530, 1992.

2 Alavanja, M.C.R., Brownson, R.C., Boice, J.D., and Hock, E., "Preexisting Lung Disease and Lung Cancer Among Nonsmoking Women," American Journal of Epidemiology 136(6): 623-632, 1992.

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**Talking Points**

- This study is based on one of the largest series of nonsmoking lung cancer cases ever assembled. The relatively large sample size is a positive aspect of the study. However, the study is also marked by a high proportion of surrogate respondents among cases, incomplete histological confirmation, and the presentation of multiple analyses.

- The magnitude of the risk associated with the highest level of saturated fat intake reported in this paper (over 6.0), and also with lower levels of consumption (1.8 to 2.8), suggests that dietary saturated fat should be considered to be a potential confounding factor or independent risk factor in studies reporting an association between spousal smoking and lung cancer.

  In comparison to the point estimate of 6.14 for the highest level of saturated fat intake in the Alavanja, et al., study, the overall point estimates reported in the approximately 35 available studies on spousal smoking range from approximately 0.7 to 2.5.

- The Brownson, et al., (1992) spousal smoking study, based on the same data set, claims that "dietary beta carotene" and "dietary fat" were considered among a number of potential confounders in the ETS analyses, but apparently only age, active smoking, and previous lung disease were adjusted in calculating risk estimates for ETS. Moreover, it is not clear how "dietary fat," as used by Brownson, et al., corresponds to "saturated fat," as used by Alavanja, et al.

  None of the other spousal smoking studies evidently included an adjustment for dietary fat intake.

- The Alavanja, et al., study adds to the existing body of literature suggesting that dietary factors may be related to lung cancer risk.

**Analysis: Methods**

Cases were nonsmoking white women between the ages of 30 and 84 with primary cancer of the lung, registered with the Missouri Cancer Registry between June 1, 1986 and June 1, 1991. A total of 618 women participated in the first phase of the study (a telephone interview); acceptable responses to the food frequency

questionnaire were provided by 429 women, who were included in the dietary analyses.

"Nonsmokers" included women "who had not smoked more than 100 cigarettes or used any other tobacco products for more than 6 months in their lifetime," and former smokers, who had "ceased using all tobacco products 15 or more years prior to interview." Both groups are included in the analyses in the paper, although the authors comment (p. 1907):

> The effect of previous smoking is seen in this study of current nonsmokers, since the proportion of former smokers was approximately twice as large among case subjects (32%) as control subjects (17%) [difference reportedly statistically significant at] (P<.0001).

Histological confirmation was available for 333, or 77% of the cases. The distribution of cell types among the cases was as follows: 49% adenocarcinoma, 28% "other pathologically confirmed tumors," and 23% for whom cell type information was missing.

Controls were randomly selected from Missouri driver's license files, and from lists provided by the Health Care Financing Administration. Controls were frequency-matched on number and age distribution to cases, at a ratio of approximately 2.2 to 1. The telephone interview was completed by 1,402 controls, and acceptable diet responses were received from 1,021.

The dietary data were obtained from a 60-item, self-administered questionnaire designed to "characterize the subject's usual diet approximately 4 years prior to the investigation."

For cases, next-of-kin who were "familiar with the woman's diet" were interviewed if the case had died or was too ill to participate. Such proxy responses were obtained for 250 (58%) of the cases.

The corresponding percent of proxy respondents among controls was only 2%. This dramatic difference in respondent type is statistically significant (P<.0001), and was considered by the authors in their analyses. They report that they conducted analyses using only the data obtained by self-report, and that "[n]o statistically significant differences were observed in any of the analyses."

**Analysis: Reported Results**

Dietary intake of the nutrients studied was divided into "quintiles," that is, five levels of intake, ranging from low to high. Thirty-six sets of quintiles were defined on the basis of total intake of each dietary component, percent of calories from each nutrient, and weekly servings of each food type. The authors note that "quartiles" are more commonly used in this type of study (p. 1912).

The authors report on univariate analyses of their data, in which a single variable was considered as a potential lung cancer risk factor. These regression analyses took into account age, previous smoking, type of interview, total caloric intake, and the individual dietary factor. The authors comment (p. 1907) that:

> Passive smoking did not affect risk estimates in this study and, therefore, was not used in any regression analysis of dietary factors.

In the univariate analyses, the following nutrients were reportedly statistically significantly associated with increased lung cancer risk: daily intake of total fat, daily intake of saturated fat, percent of calories from fat, percent of calories from saturated fat, and weekly servings of citrus fruit. Statistically nonsignificant positive associations were reported for daily intake of oleic acid, weekly servings of red meat, and weekly servings of dairy products.

A statistically significant decreased risk was reported for the intake of fiber from beans and peas, weekly servings of beans and peas, and weekly servings of fruits other than citrus. Statistically nonsignificant decreases were reported for percent of calories from carbohydrates, and weekly servings of fish and chicken.

The authors report that their various measures of dietary fat were highly correlated with one another. Analyses of individual factors while controlling for the others resulted in only the effect of saturated fat remaining "highly significant"; the significance of the other measures of fat intake "disappeared" following adjustment for saturated fat consumption.

Additional multivariate analyses (considering more than one factor simultaneously) were developed. In these analyses, additional dietary factors became statistically nonsignificant.

The final multivariate model included daily intake of saturated fat, weekly servings of beans and peas, and weekly servings of citrus fruits and juice.

The reported risk estimates for daily intake of saturated fat, generated from the final model, were as follows. The baseline for comparison (quintile 1) was women who consumed 111 calories or less from saturated fat daily. For quartile 2 (112-146 saturated fat calories), the reported risk estimate was 1.65 (95% CI 0.94-2.91); for quartile 3 (147-185 calories), 1.81 (95% CI 0.96-3.42); for quartile 4 (186-237 calories), 2.83 (95% CI 1.35-5.94; statistically significant); and quartile 5 (237 or more calories), 6.14 (95% CI 2.63-14.40; statistically significant).

When the authors restricted the analysis to adenocarcinoma cases alone, the reported risk estimates were even higher, and all statistically significant: quintile 2, 2.14 (95% CI 1.02-4.48); quintile 3, 2.77 (95% CI 1.21-6.39); quintile 4, 4.30 (95% CI 1.62-11.3); and quintile 5, 11.38 (95% CI 3.77-34.4). The sample size decreased in these analyses, and the confidence intervals are substantially wider than those based on the entire study population.

For weekly servings of beans and peas, risk estimates were consistently less than 1.0, suggestive of a decrease in risk associated with consumption of these foods. Interestingly, the risk estimates were of approximately the same magnitude regardless of quintile division. However, Appendix Table 1, the list of quintiles, does not present the quintile breakdown for this index, so it is not possible to examine these risk estimates with respect to the number of weekly servings associated with them.

As acknowledged by the authors, their results for citrus fruit and juice consumption are "surprising," as they suggest an increased risk associated with increasing consumption (p. 1912). These risk estimates range from approximately 1.2 to 2.2. Conventionally, it is believed that increased consumption of citrus and other fruits should be associated with a decrease in cancer risk. The authors offer two possible explanations for their results: that lung cancer patients tended to consume more citrus fruits than did persons without the disease, possible in response to symptoms of lung disease prior to diagnosis of lung cancer, and that the "protective" effect reported elsewhere was limited to cell types other than adenocarcinoma, which dominated this case series (p. 1912).

**Potential Criticisms**

- The quintile breakdown for calories from saturated fat is not the same as the quintile breakdown for percent of calories from saturated fat. Thus, the reported risk estimates do not lend themselves to interpretation according to percentage of calories from dietary fat. In Appendix Table 1, the authors do present quintile breakdowns for percent of calories from fat and from saturated fat. These indicate that the highest quintile for percent of calories from fat, which may or may not correspond to the highest quintile for calories from fat, included women who consumed, on average, as much as 42.5% of their caloric intake as fat, and as much as 12.5% as saturated fat. Current suggested dietary guidelines recommend that approximately 30% or less of total calories come from fat, and approximately 10% or less from saturated fat.

- This paper, with its numerous divisions of the study population, and large number of analyses, illustrates the practice of "data-dredging," or multiple comparisons. The authors acknowledge (p. 1913):

> [W]ith numerous food groups and nutrients being examined, we cannot rule out the possibility that our results could be due to chance alone. Because of the high intercorrelations among many of the dietary variables, we felt it would be overly conservative to adjust the P values for the effect of making multiple comparisons. However, we do realize that high correlations are no guarantee against occasional spurious 'significant' results when large numbers of comparisons are made, so we recommend careful interpretation.

- An editorial, published at the same time (Kolonel, 1993), questions whether the models employed by Alavanja, et al., are appropriate:[3]

> When variables that are highly collinear [sic] [correlated] are included in a model, as is

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[3] Kolonel, L.N., "Lung Cancer: Another Consequence of a High-Fat Diet?" Journal of the National Cancer Institute 85(23): 1886-1887, 1993.

> the case in the study by Alavanja et al., invalid and unexpected results can occur. Even in the authors' subsequent analyses, in which saturated fat and total calories were included in the models, the results could be misleading.

- The high number of surrogate respondents among cases (58%) is a potential source of bias, as next-of-kin might be expected to be less knowledgeable about someone's diet than would be the person herself. However, the authors claim that their analyses taking respondent type into account provide "adequate protection against any bias from including next-of-kin food frequency reports."

- In his editorial, Kolonel makes the following comment:

> [T]he addition of lung cancer to the health consequences of a high-fat diet . . . is hardly needed to strengthen the arguments for taking aggressive public health measures to lower the average fat level in the American diet. . . . [O]ne might ask, does the identification of secondary risk factors for lung cancer play into the hands of the tobacco industry, which grasps at these straws in its relentless efforts to diminish the significance of cigarette smoking as the overwhelming worldwide cause of lung cancer?